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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/714,564

11/14/2003

Orest W. Blaschuk

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07/05/2006

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EXAMINER

HADDAD, MAHER M

ART UNIT

PAPER NUMBER

1644

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/714,564

Applicant(s)

BLASCHUK ET AL.

Examiner

Maher M. Haddad

Art Unit

1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-101 is/are pending in the application.
- 4a) Of the above claim(s) 3,4,8,16,17 and 19-101 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-2, 5-7, 9-15 and 18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/21/05</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION

1. Claims 1-101 are pending.
2. A clear and obvious typographical error occurred in the restriction wherein claim 8 which reads on a cyclic peptide was not included a linking claim of Group III. Claim 8 read only on non-elected Group IV.
2. Applicant's election of Group III, claims 1-2, 5-7, 9-15 and 18 directed to a cell adhesion modulating agent comprises SEQ ID NO:2 or conservative analogue thereof, wherein the peptide present within a linear peptide filed on 5/1/06, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
3. Claims 3-4, 8, 16-17 and 19-101 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.
4. Claims 1-2, 5-7, 9-15 and 18 are under examination as they read on a cell adhesion modulating agent comprises SEQ ID NO:2 or conservative analogue thereof, wherein the peptide present within a linear peptide.
5. Applicant's IDS, filed 4/21/05, is acknowledged.
6. Claim 1(i) is objected to because the acronym CAR should be inserted after the recitation of "cell adhesion recognition" (CAR) in line 1 of claim 1(i).
7. Claim 7 is objected to under 37CFR 1.821(d) for failing to recite the SEQ ID NOS. in the claims.
8. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim 1(B) and claim 7 contain four amino acid sequences fail to comply with the sequence rule.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1644

9. Claims 1-2, 5-7, 9-15 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- A. The sequence “Arg-Trp-Ala-Pro-Ile-Pro (SEQ ID NO: 2)” recited in claim 1(B) is indefinite because the sequence listing list SEQ ID NO: 2 as pentapeptide Trp-Ala-Pro-Ile-Pro, which does not correspond to Arg-Trp-Ala-Pro-Ile-Pro.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-2 and 5-7 and 9-15 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cell adhesion modulating agent comprising a Trp-containing cell adhesion recognition (CAR) sequence of desmosomal adhesion molecule but consist of no more than 50 consecutive amino acid residues present within the desmosomal cadherin molecule, wherein the CAR sequence is SEQ ID NO: 2 or RWAPIP, does not reasonably provide enablement for any cell adhesion modulating agent that (a) modulates desmosomal cadherin-mediated cell adhesion; and (b) comprises (i) a Trp-containing cell adhesion recognition sequence of an desmosomal cadherin molecule, but “contains no more than 50 consecutive amino acid residues present within the desmosomal cadherin molecule, wherein the Trp-containing CAR sequence is (B) the amino acids sequence Arg-Trp-Ala-Pro-Ile-Pro (SEQ ID NO:2); (ii) a conservative analogue of SEQ ID NO: 2 in claim 1, wherein the cell adhesion modulating agent is a “conservative analogue” of SEQ ID NO: 2 in claim 9; wherein the peptide comprises an N-terminal or C-terminal “modification” in claim 10, the cell adhesion modulating agent of claim 1 linked to a “heterologous compound” in claim 12, wherein the heterologous compound is a “pharmaceutically active compound” in claim 13, the cell adhesion modulating agent of claim 1 further comprising a “cell adhesion recognition” sequence other than SEQ ID NO: 2, wherein the cell adhesion recognition sequence is separated from SEQ ID NO: 2 by a linker in claim 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

After a review of the specification with respect to the nature of “conservative analogue”, the specification was not found to provide sufficient guidance to the skilled artisan as to how to make and use SEQ ID NO: 2 “conservative analogs” commensurate in scope with the instant claims. Given the breadth encompassed by the instant claims, Applicant has not provided the

Art Unit: 1644

skilled artisan with sufficient guidance as to the identity of all residues to be changed, to be left unchanged, to be deleted, or to have additional (unidentified) sequences inserted between. Without clear direction and guidance as to the nature of the changes made to a reference Trp-containing CAR sequence, the skilled artisan would be faced with undue experimentation to produce the immense number of “analogs” encompassed by the instant claims and determine if there were any operative embodiment that would result in the recited functional activity.

The term “comprising” is an open-ended, it expands the agent to include additional non disclosed amino acids on either or both of the N- or C- termini of SEQ ID NO: 2. Such amino acids would significantly interfere with the activity of the compound. There is insufficient guidance as to which amino acids outside SEQ ID NO: 2 would maintain the same function of binding to cadherin CAR sequence Trp-containing. It would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have the same functional activity. It would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the cell modulating agent of Trp-containing CAR. Without sufficient guidance, the changes which can be made in the structure of “SEQ ID NO:2” and still provide an active Trp-containing CAR peptide sequence is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Figure 6 of the specification discloses the effect of ADH358, claimed SEQ ID NO: 2 (peptide derived from desmocollin) on SKOV3 Human Ovarian Cancer Cells. The peptide caused disruption of the confluent SKOV3 monolayers within 24 hours of addition to the tissue culture medium. Further the peptide caused the SKOV3 cells to detach from one another and adopt an elongated, fibroblast-like morphology. The specification concludes that the Trp-containing peptides can disrupt cell adhesion (see page 148, lines 11-16). Table II lists RWAPIP to be present in all desmocollin species. However, one cannot extrapolate the teachings of the specification to the scope of the claims because the agent that “modulates desmosomal cadherin-mediated cell adhesion” are peptides that have mutually exclusive function. The specification only discloses that the claimed SEQ ID NO: 2 can disrupt cell adhesion. The skilled artisan would not know which peptide can be used to enhance cell adhesion. Those cell adhesion-modulating activity are mutually exclusive in that they reach opposing endpoints. It has not been shown that these peptides are capable of functioning as that which is being claimed. The skilled artisan would not have a reasonable expectation that the same methodology used to disrupt cell adhesion would also serve to enhance cell adhesion either in general or to obtain the desirable endpoint.

There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would use the multifunctional modulating agents comprising a Trp-containing CAR sequence recited in the instant claims. Due to the contradictory and seemingly mutually exclusive activity of the claudin CAR sequences, undue experimentation would be required of the skilled artisan to determine the effect of claudin CAR sequences on any particular cell adhesion response in view of the instant disclosure.

Art Unit: 1644

Regarding the “modification” recited in claim 10, the specification fails to provide the kind of modifications that can be introduced to the N- or C terminus of the peptides and still have the claimed function.

Claim 12-13 recites that the modulating agent is linked to pharmaceutically active compound. It appears that applicant is using the modulating agent for target delivery of a drug. However, in view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the modulating agent as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed modulating agent are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed modulating agent with a reasonable expectation of success.

Claim 15 recites that the Trp-containing CAR sequence further comprising any “adhesion recognition sequence other than SEQ ID NO:2” using a linker. However, the skilled artisan would not know what other adhesion recognition sequences can be linked to claimed agent and how to use the resultant chimera.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-2, 5-6, 9-10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/10258 (IDS Ref. No. BK).

The '258 publication teaches a compound comprises a region of the desmosomal cadherin (Dsc2) RWAPIPCSMML or RWAPIPCSMQ (Dsc3) peptide (see page 4 under Dsc2 and Dsc3 in particular). The two amino acids sequences are Trp-containing and contain no more than 50 consecutive amino acid residues. The two peptide sequences are present within a linear peptide, the compound comprises a peptide which is 10 amino acids (i.e., ranging in size from 6-50/6-15 amino acid residues). The peptide comprises an N-terminal and C-terminal modification. The RWAPIP is lined to a heterologous compound CSML.


The agent of instant claims is included because the agent reads on a compound without a carrier.

Art Unit: 1644

While the prior art teachings may be silent as to the “modulates desmosomal cadherin-mediated cell adhesion” per se; the products the reference are the same as the claimed products. Therefore “modulates desmosomal cadherin-mediated cell adhesion” is considered inherent properties.

The reference teachings anticipate the claimed invention.

14. Claims 1-2, 9-10 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Chidgey et al (Developmental Dynamics 210:315-327, 1997).

Chidgey et al teach a compound comprises the n-terminus of mature Dscs, WAPIP (see page 316, 2nd col., 1st full paragraph in particular). The amino acid sequence is Trp-containing which contain no more than 50 consecutive amino acid residues. The peptide sequence is present within a linear peptide. Chidgey et al further teach the EC1 domain of the DSC1-3 (see fig. 3), wherein the RWAPIP conserved sequence peptide comprises a C-terminal modification. The C-terminal additional amino acids are considered a heterologous compound. The heterologous compounds is a pharmaceutically active compound because it contains a putative cell adhesion recognition site which is YAT (indicated with ) (see Fig. 3 in particular). Finally, the term “comprising” no more than 50 consecutive amino acids would open the claim up to read on the EC1 domain taught by the Chidgey et al reference.

The agent of instant claims is included because the agent reads on a compound without a carrier.

While the prior art teachings may be silent as to the “modulates desmosomal cadherin-mediated cell adhesion” per se; the product in the reference is the same as the claimed product. Therefore “modulates desmosomal cadherin-mediated cell adhesion” is considered inherent properties.

The reference teachings anticipate the claimed invention.

15. Claims 1-2, 5, 7, 9, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by WO94/21809.

’809 publication teaches a compound comprises Thr Val Leu Arg Arg Ala Lys Arg *Arg* Trp Ala Pro Ile Pro Cys Ser (see page 47, line 14 in particular). The amino acid sequence is Trp-containing and contain no more than 50 consecutive amino acid residues. The peptide sequence are present within a linear peptide, the compound comprises a peptide which is 16 amino acids (i.e., ranging in size from 6-50 amino acid residues). The peptide comprises an N-terminal and C-terminal modification. The RWAPIP is linked to a heterologous compound Thr Val Leu Arg Arg Ala Lys Arg *Arg*.

The agent of instant claims is included because the agent reads on a compound without a carrier.

Art Unit: 1644

While the prior art teachings may be silent as to the “modulates desmosomal cadherin-mediated cell adhesion” per se; the products used in the reference are the same as the claimed claimed. Therefore “modulates desmosomal cadherin-mediated cell adhesion” is considered inherent properties.

The reference teachings anticipate the claimed invention

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/10258 (IDS Ref. No. BK), Chidgey et al OR WO94/21809 each in view of in view of U.S. Patent No. 5,455,228.

The teachings of the WO '258 Chidgey et al and WO94/21809 have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation the peptide comprises N-terminal modification which is N-acetylation in claims 10-11.

The '228 patent teaches the acetylation of the N-terminus is the traditional method for producing a peptide that resists cleavage by aminopeptidase M (col., 2, lines 38-42 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to N-acetylate the peptide agent taught by the WO '258 Chidgey et al or WO94/21809 as taught by the '228 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because to resist cleavage by aminopeptidase M as taught by the '228 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Art Unit: 1644

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 1 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/10258 (IDS Ref. No. BK), Chidgey et al OR WO94/21809 each in view of in view of U.S. Patent No. 6,936,587.

The teachings of the WO '258 Chidgey et al and WO94/21809 have been discussed, *supra*.

The claimed invention differs from the reference teachings only by the recitation that the agent is linked to a solid support in claim 14.

The '587 patent teaches that the peptide bound to a solid support, is used to enrich or purify specific antibodies (col., 20, lines 56-67 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to link the peptide taught by the WO '258 Chidgey et al or WO94/21809 to a solid support as taught by the '587 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so to enrich or purify specific antibodies as taught by the '587 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claims 1 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/10258 (IDS Ref. No. BK), Chidgey et al OR WO94/21809 each in view of in view of U.S. Patent No. 6,713,450.

The teachings of the WO '258 Chidgey et al and WO94/21809 have been discussed, *supra*.

The claimed invention differs from the reference teachings only by the recitation that the agent in combination with a physiologically acceptable carrier in claim 18.

The '450 patent teaches the synthetic peptides, or conjugates thereof, can be formulated as an immunizing composition using adjuvants, pharmaceutically-acceptable carriers, excipients, diluents, auxiliary agents or other ingredients routinely provided in immunizing compositions. Such formulations are readily determined by one of ordinary skill in the art and include formulations for immediate release and for sustained release, e.g., microencapsulation (col., 12, lines 53-67 in particular).

Art Unit: 1644

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the peptide agent taught by the WO '258 Chidgey et al or WO94/21809 into a composition using pharmaceutically-acceptable carriers as taught by the '450 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Such formulations are readily determined by one of ordinary skill in the art and include formulations for immediate release and for sustained release as taught by the '450 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 9, 2006

Maher Haddad
Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600

Notice to Comply

Application No.

10/714,564

Examiner

Maheer M. Haddad

Applicant(s)

BLASCHUK ET AL.

Art Unit

1644

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other: Claim 1(B) and claim 7 contain four amino acid sequences fail to comply with the sequence rule.

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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